Index

A

AADvac1, 75 ABBV-8E12, 76 Abeotaxane (TPI-287), 73 ABvac40, 29 Acetylcholine, 11, 156, 170, 171, 182, 192, 194 Acetylcholinterase (AChE) AD treatment, use in, 170 amyloid plaques, production of, 171, 176 amyloid-beta accumulation, relationship between, 11 binding pocket, 174 catalytic site of, 174, 176 enzymes, 183 inhibitors, 71, 156, 171, 172, 173, 174, 175-176, 177, 185-187, 189, 192, 196-197, 198, 208 NFTs, role in producing, 171 retaining, 172 ACI-24, 29, 31 ACI-35, 75 Aducanumab (BIIB037), 24, 39-40, 157 Affitope AD02, 31 Aging, as rick factor for AD, 137 Akt, 103, 104, 105, 106, 112 Aluminum (Al), 31, 84, 86 Alzheimer Association, 100 Alzheimer, Alois, 2 Alzheimer's disease blood-brain barrier. role of (see blood-brain barrier)

characteristics of, 2, 151 decline, 6, 108 diabetes, relationship between (see diabetes) environmental factors, 152 epigenetic modifications in (see epigenetics in AD) etiology (see etiology of Alzheimer's) genetics, role of (see genetics, Alzheimer's) inflammation, role in Alzheimer's (see inflammation, role in Alzheimer's) manifestations of, 2, 3 neurodegeneration, 8, 52, 71, 73, 75, 77, 90, 120, 169 neuroinflammatory changes, 70, 92 neuropsychiatric manifestations, 166-167 nondiabetic, 102, 103, 104, 106, 112 (see also diabetes) overview, 70, 135, 136, 165, 166, 181 pathogenesis (see pathogenesis, Alzheimer's disease) pathogenic mechanisms, 62 pathology, 166, 167 preclinical, 29, 71, 120, 159, 198 preclinical drug candidate, 34, 192 prevalence (see prevalence, Alzheimer's disease) progression, 160 risk factors, 2 stages, 2, 6, 77, 155 synaptic losses, 168

AMPK, 109 Amyloid cascade hypothesis, 11, 24, 51, 52, 167-168, 181, 185 Amyloid precursor protein (APP), 83, 85-86, 90, 108, 120, 167-168 Amyloid β40 (Aβ40), 29, 36–37, 52, 54, 57-58, 152, 168, 215 Amyloid β42 (Aβ42), 58, 60–61, 89, 108, 111, 112, 152, 167-168 Amyloid- β , 85, 119. *See also* amyloid- β plaques amyloid hypothesis (see amyloid cascade hypothesis) antiaggregation effects, 187–188 antimicrobial properties, 156 inhibitors, 188-189 metal-binding properties, 87 peptides, 25, 108, 112, 156, 181 Amyloid- β plaques, 1, 5 aggregation in brain, 52, 87, 166 amyloid hypothesis (see amyloid cascade hypothesis) binding affinity, 37 brain, accumulation in, 24, 51-52, 153 diffuse, 166 immunotherapy, 77 increases of, in diabetics, 100 metals, relationship between, 86 reducing, 38, 40, 52 role of, in AD, 41, 140, 151, 152 tau proteins, combination therapy directed to, 79 vasculature surrounding, 143 AN1792 vaccine, 28, 29 APKC, 99, 103, 104, 105, 106, 107, 110, 112. See also hepatic aPKC activators, 100, 111 brain activity, 101 inhibitors, 108-110

memory function, relationship between, 110-111 recombinant, 108 Apolipoprotein E gene ε 4 allele (APOE ε4), 120, 140, 145, 157 Apolipoproteins E (ApoEs), 70, 140, 153, 154 AstraZeneca, 41 Astrocyte cell culture model, 118 Astrocytes, 4, 120, 123, 125, 127, 138, 141, 153, 168, 169, 211 ATP-binding cassette (ABC) transporters, 118 Atypical protein kinase C, 99, 100–101 Aurothiomalate [ATM], 105, 106 Autophagy lysosome pathway, 11 AZP2006, 72 A β plaques. See amyloid- β plaques A β precursor protein (APP), 3, 24, 25

B

BACE1 mRNA, 108 Bacopa, 205, 209, 211-213 BAN2401, 38-39, 157 Bapineuzumab, 34 BAPTA, 89 Benzyl piperidone, 173-174 Berberine, 205, 206, 215 Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), 100, 103, 106, 107, 108 AD, role in pathogenesis of, 101–102 inhibitors, 158, 185-186, 187 interactions with, 191 levels, 101 processing APPs, role in, 185 regulating, 160 Bioavailability of drugs, 128

Biogen, 40 Blood-brain barrier, 73, 84, 89, 106 AD-related changes, 120-121 brain endothelial cells (BECs) (see brain endothelial cells (BECs)) cognitive impairment, as marker of, 140 damage, 145 defining, 117 description, 136 deterioration, 137 disruption, 137 drug delivery across, 118, 127–128, 128-129 dysfunction, in AD, 127, 128, 129 focused ultrasound use, 128 human versus rodent, 122 immune responses, 118 integrity of, 118, 125, 136 leakage, 120, 140 models, 2D, 125 models, 3D, 126-127 neuroimmunity, 138 organoids, 127 overview, 117, 118-120 penetrating, 187 permeability, 122, 135, 139, 194, 197 preclinical models, 125 SPARC effect on, 141, 142-143 in vitro model development, 117, 123, 125, 126, 129 Brain endothelial cells (BECs), 118 degeneration, 120 iBECs. 124 immortalized, 123, 124 primary, 123, 124 Brain's default mode network (BDMN), 153 Breast cancer resistance protein (BCRP), 118 Butyrylcholinesterase (BuCHE), 184

С

C-terminal fragments (CTFs), 55, 57 Cadmium (Cd), 84, 86-87 Calcium (Ca), 87 Calcium channel blockers (CCBs), 176-177 Cannabinoid receptors, 195 Canosine, 59 Capsaicin, 205, 214-215 Carrier mediated transport (CMT), 118 Cascade hypothesis, 24 Ceramide, 104 Cerebellum, 168 Chelators, metal, 52, 59, 86, 89, 90, 91, 170 Chimeric conjugates, 165, 172, 175-176 Cholinergic hypothesis, 11, 52, 169 Cholinergic neurotransmission, 192-194 Cholinesterase inhibitors, 24, 155, 165, 170, 182, 189 Cholinoesterases, 196 Clinical trials, ethical standards for, 78 Clinioquinol (CQ), 89 Cobalt (Co), 87, 90 Conventional PKCs (cPKCs). 107–108 Convolutional neural network (CNN) algorithm, 145 Copper (Cu), 84, 86, 87, 88, 89, 170 Copper-bis(thiosemicarbazonoto), 90 Crenzumab, 35 CRISPR. 128 Curcumin, 205, 206, 213-214 Cysteine, 86

D

DAG-activated cPKCs, 107–108 Davunetide peptide, 81 Dementia. *See also* Alzheimer's disease Dementia forms, 1 Diabetes copper overload, 89 hyperinsulinemia, 99-100, 101, 104-105, 106, 112 insulin receptors (IR), 102, 103, 104.112 insulin-resistant, 99, 101, 102, 106 insulin-resistant Alzheimer's disease, 100 liver, insulin action in, 103 metabolic syndrome (MetS) (see metabolic syndrome (MetS)) obesity/type-2-diabetic (O/T2D) states, 99, 102, 103, 105, 109, 111, 112 (see also obesity) pre-diabetes, 102, 103 type 2, 100, 102, 103 Diagnosis, Alzheimer's disease, 53 Disability Assessment for Dementia (DAD), 34 DNA methyltransferases, 151, 154 DNA-demethylating agents, 158 Dominantly Inherited Alzheimer Network (DIAN) trial, 38 Donecopride, 192 Donepezil, 170, 171, 172-174, 182, 185, 187, 195, 196 Down Syndrome, 4, 31, 213 DP-109,89 Drug delivery systems (DDSs), 91 Drug reactions, adverse, 206 Dystrophic neurites, 152

E

Early-onset Alzheimer's disease (EOAD), 3, 24 Endothelial cells, brain. *See* brain endothelial cells (BECs) Enzyme inhibitors, 196 Epigenetics in AD anti-amyloid-β therapies, 157 brain evolution, role in, 155 changes in, 151, 156, 160 changes, reversing, 156 gene modulation, 154, 158 therapies, 156–161 Epothilone D, 73 Etiology of Alzheimer's, 2, 3–5. *See also* genetics, Alzheimer's Excitotoxicity, 92

F

Flavinoids, 214 Flubiprofen, 197 Fluorination, 53 Focused ultrasound (FUCs), 128 Free radicals, 170 Fyn tyrosine kinase, 72

G

G protein-coupled receptors (GPCRs), 184, 192, 194, 198 Galantamine, 155, 170, 182 Gantenerumab, 31–32, 36, 38 Genentech, 35 Genetics, Alzheimer's environmental factors, interaction between, 152 factor in AD cases, 2 gene mutations, 24–25 inherited forms, 1, 3, 70 Mendelian inheritance, 3 mutations, 3 risk factors, 3–4 Ginkgo biloba, 205, 206–207, 207–208 Glucose transport, 137 Glycogen synthase kinase-3 (GSK-3), 72 GSK-3β, 86, 189, 190, 191

H

HDAC inhibitors (HDACis), 158-159 Hepatic aPKC, 106. See also aPKC Hevin, 136, 141, 143 Hippocampus, 152, 158, 160, 167 Histone acetylation, 151, 157–158 Histone acetyltransferases (HATs), 155.160 Histone deacetylases (HDACs), 155 Histone H4 with acetylation at the 16th lysine residue protein (H4K16ac), 157 - 158Homeostasis, brain, 136 Homeostasis, metal. See metal homeostasis Huntington's chorea, 213 Hyper-phosphorylated tau, 129 Hyperinsulinization, of brain, 106 Hyperosmosis, 127 Hyperphosphorylation of tau proteins. See Tau proteins

I

IBECs, 124, 127 ICAP, 109, 110 ICAPP, 109 IL-1 β , 108, 111, 187 Immunotherapy strategies ABvac40, 29–30 ACI-24, 29, 31 active-A β -directed strategies, 28–29 Affitope AD02, 31 anti-A β strategies, 24, 25–28 antibodies, clinical trials, 24

BAN2401, 38-39 bapineuzumab, 34 crenzumab, 35 gantenerumab, 36, 38 MEDI1814, 40-41 monoclonal antibodies, passive immunotherapy with, 31-32 ponezumab, 36-37 SAR228810, 41 solanezumab, 37-38 UB 311. 31 vaccines (see vaccines, for AD) Induced pluripotent stem cell, 118, 124 - 125Inflammation, role in Alzheimer's, 4, 10, 75, 104 Inherited forms of Alzheimer's. See genetics, Alzheimer's Insulin resistance, brain, 102 Insulin, role in AD, 9, 10 Interlaminar astrocytes, 123 Intravenous immunoglobulin (IVIg), 75,76 Ionophores IPSCs, 124, 128 Iron (Fe), 84, 86, 87, 90, 170

K

Kaempferol, 205, 214 Keyhole limpet cyanine (KHL) carrier proteins, 29

L

L-peptides, 57 Late-onset Alzheimer's disease (LOAD), 3 Lead (Pb), 84 Limbic system, 152

M

Machine learning (ML) algorithms, 144 Magnesium (Mg), 87 Mammalian target of rapamycin (mTOR), 104 Manganese (Mn), 84, 86, 87 Mannitol. 127 MAOs (MAO-A and MAO-B), 196 MAP kinases, 86 MEDI1814. 40-41 Memantine, 156, 170, 172, 182 Mendelian inheritance, 3 Met 35, 53-54 Metabolic syndrome (MetS), 100, 103, 105. 106. 111. See also diabetes Metal chelators. See chelators, metal Metal homeostasis, 83, 87-88 Metal hypothesis, 191 Metal imbalance hypothesis, 182 Metal ion hypothesis, 170 Metal protein attenuating compounds (MPACs), 88-89, 90 Metal-binding proteins, 84 Metal-focused interventions. See trace metals Metallochaperones, 84, 87-88, 90 Metals, trace. See trace metals; specific metals Meynert, 152 Microglia, 138, 141, 187 MicroRNA expression, 151 Microtubule-associated protein tau (MAPT), 5, 154 Mild traumatic brain injury (mTBI), 139-140 MiRNA, 160 Molybdenum (Mo), 87 Monoclonal antibodies, 31-32

MRNA, 111 Multidrug resistance-associated proteins (MRPs), 118 Multitarget-directed ligands (MTDLs). *See* multitargeted ligands (MTLs) Multitargeted ligands (MTLs), 182, 183–185 cholinergic inhibition, 194–195 cholinergic neurotransmission, 192–194 cholinesterases, targeting, 195 endocannabinoid system, targeting, 195 H3R antagonism, 194–195 serotonic, influence on, 192

Ν

N-benzylpiperidine, 185-186, 187, 193, 196 N-methyl-D-aspartate (NMDA) antagonists (glutamate inhibitor), 170, 171-172 N-methyl-D-aspartate (NMDA) neurotransmissions, 184 N-methyl-D-aspartate (NMDA) receptor antagonists, 71, 182 N-methyl-D-aspartate receptor agonist, 24 N-methylation, 53 Namzaric, 182 Nanomedicine, 83 Natural substances, use in AD. See also specific substances drug interactions, 205 overview, 205 Paquid study, 208–209 Neocortex, 6 Neurocognitive disorders, definition, 206, 215

Neurodegeneration in Alzheimer's, 1, 169.170 Neurofibrillary tau tangles (NFTs), 1, 2, 5-6, 86, 92, 140, 151, 152, 166, 167.169 formation, 8 Neuroimmunity, 138 Neuroinflammation, 138-139 Neuropathology of Alzheimer's autophagy lysosome pathway, 11 A β plaques (see amyloid- β plaques) cholinergic hypothesis, 11 hypoglycemia, 10 inflammation, role in Alzheimer's (see inflammation, role in Alzheimer's) insulin, 9, 10 mitochodrial dysfunction, 9 neurofibrillary tau tangles (NFTs) (see neurofibrillary tau tangles (NFTs)) overview. 5 oxidative stress. 9 ubiquitin-proteasome system (UPS), 10 - 11vascular dysfunction, 10 Neuroplasticity, 153 Neurovascular unit (NVU), 118 NFKB, 108, 111-112 NMDA receptors, 7 NOR tests, 111 Novartis, 29 Nutritional interventions, AD, 87 NVU, 124

0

Obesity, 102, 103, 104, 106. See also diabetes Oligodendrocytes, 168 Oligomers, 7 Oxidative stress, 87, 104, 153, 169–170, 182

P

P-glycoprotein (P-gp), 118 Paired helical fragments (PHFs), 6 PAMPA, 196 Parkinson's disease, 213 Pathogenesis, Alzheimer's disease APP, 7-8 Aβ, 7–8 complexity, 196 hallmarks of, 182 NFTs, 8-9 overview. 7 pathogenic mechanisms, 62 tau, 8–9 Penicillamine, 90 Peptides Alzheimer's disease, use as strategy for. 52 inhibitors (see peptidic inhibitors) library screening, 59-61 Peptidic inhibitors A β peptide inhibitors, 54, 57–58, 61 - 62non-A β -based peptide inhibitors, 59 overview, 53-54 Pericytes, 118, 120-121, 125, 127 Peripheral endothelial cells, 118 Phage display, 59 Phagocytes, 25 Phosphatidic acid (PA), 104 PKC-δ, 108 PKC-λ, 108, 109, 111 PKMζ, 109, 110, 111

Polymeric nanoparticles, 91 Polypharmacology in AD. See also specific drugs drugs used, 182 multifunctional agents, 185-188 multitargeted ligands (MTLs) (see multitargeted ligands (MTLs)) Ponezumab. 36-37 Post-mortem histopathology of Alzheimer's, 6 Potassium (K), 87 Pre-diabetes. See diabetes Presenilin 1 (PSEN1), 3, 24, 120, 168 Presenilin 2 (PSEN2), 3, 24, 168 Prevalence, Alzheimer's disease, 2, 24, 52, 70, 100, 166 Proline (Pro), 86 Protein-fragment complementation assay (PCA), 81 Pyrrolidine dithiocarbamate (PDTC), 90

Q

Quercetin, 205, 206, 214

R

RAWM tests, 111 Reactive oxygen species (ROS), 206 Receptor-mediated transcytosis (RMT), 118 Reelin, 154–155 Repressor element 1-silencing transcription factor (REST), 157 Resveratrol, 205, 206, 213 Retro-inverso cyclization, 53 Rivastigmine, 170, 171, 172, 174–175, 182 Rottlerin, 107

S

Sanofi, 41 SAR228810, 41 Saracatinib, 72 Secreted protein acidic and rich in cysteine (SPARC) protein, 135-136, 140-141, 142-143, 144, 145 Serine (Ser), 86 Serotonin, 192-193 SHANK proteins, 92 Shogaol-huprine hybrids, 189 Short-term memory decline, 1 Sodium (Na), 87 Solanezumab, 37-38 SPARC. See secreted protein acidic and rich in cysteine (SPARC) protein Sulforaphane, 159 Synaptophysin, 89

T

T-cells, 25-26 Tacrine, 170, 171, 172, 175-176, 191, 193, 198 Tau hypothesis, 168-169, 182 Tau proteins aggregation prevention, 73-74, 188.189 Alzheimer's disease, as factor in, 71 amyloid, combination therapy directed to, 79 antibodies, 76, 77 hyperphosphorylation, 86, 90 immunotherapy, 74-76, 77 impact of incorrect levels of, 8-9 inhibitors, 188-189 isoforms of, 8 metal-binding properties, 87

neuropathophysiological functions, 77 p-Tau, 34, 106 PET imaging of, 74 phosphorylation, 72 protein hypothesis, 52 protein therapy, 69 role of, 8 T-Tau. 34 trace metals, relationship between, 83.85 zinc, interactions with, 86 TEER, 124, 125 Tetrahydroisoquinoline-benzimidazole derivatives. 187 Threonine (Thr), 86 Tideglusib, 72 TJ proteins (TJPs), 122, 124 TNF-α, 108, 111–112, 187 Trace metals. See also specific metals Alzheimer's disease, relationship between, 84, 85, 91 deficiencies, 87 disregulation of, 84 homeostasis (see metal homeostasis) imbalance of, hypothesis (see metal hypothesis)

metal-focused interventions, 88–89 supplementation, 87 tau proteins, relationship between, 84 Transcriptional neoteny, 153 Transwell models, 125, 126 Traumatic brain injury (TBI), 139–140 Triethylenetetramine (TETA), 89, 90 Tryptophan hydroxylase, 84 Tyrosine hydroxylase, 84

U

UB 311, 31 Ubiquitin-proteasome system (UPS), 10–11

V

Vaccines, for AD, 23, 69, 74, 75. See also specific vaccines Vascular dementia, 4 Virtual screening, 136 Vitamin B3, 159

Z

Zinc (Zn), 84, 86, 87, 88, 89, 90, 91, 92

Doi: https://doi.org/10.36255/exonpublications.alzheimersdisease.2020.ind